CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

NITHIAZINE

Chemical Code # 5129, Tolerance # 52241

6/14/00

I. DATA GAP STATUS

Chronic toxicity, rat:	No study on file[1]
Chronic toxicity, dog:	No study on file[1]
Oncogenicity, rat:	No study on file[1]
Oncogenicity, mouse:	No study on file[1]
Reproduction, rat:	No study on file[1]
Teratology, rat:	No study on file[1]
Teratology, rabbit:	No study on file[1]
Gene mutation:	No data gap; no adverse effect
Chromosome effects:	No data gap; no adverse effect
DNA damage:	No data gap; no adverse effect
Neurotoxicity:	No study on file[1, 2]

Toxicology one-liners are attached.

All record numbers through 173332 were examined.
** indicates an acceptable study.
Bold face indicates a possible adverse effect.
indicates a study on file but not yet reviewed.
File name: T182476.doc

[1] New active ingredient, Nithiazine, submitted for Section 3 registration application for terrestrial, nonfood use. These studies are not required at this time.

[2] Acceptable acute neurotoxicity study in rats is on file.

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

These pages contain summaries only. Individual worksheets may contain additional effects.

COMBINED, RAT

No study submitted.

CHRONIC TOXICITY, RAT

No study submitted.

CHRONIC TOXICITY, DOG

No study submitted.

ONCOGENICITY, RAT

No study submitted.

ONCOGENICITY, MOUSE

No study submitted.

REPRODUCTION, RAT

No study submitted.

TERATOLOGY, RAT

No study submitted.

TERATOLOGY, RABBIT

No study submitted.

GENE MUTATION

** 52241-003; 173324; "Mutagenicity Evaluation of IN A0159-26 in the CHO/HPRT Assay" (Bentley, K., E.I. du Pont de Nemours and Co., Inc., Haskell Laboratory for Toxicology and Industrial Medicine, Newark, Del., Project ID No. 231-90, 5/14/90). Chinese hamster ovary cells (CHO-K1 clone BH_4) were exposed to test article A0159-26 (Haskell No. 18243, > 99% pure) at concentrations ranging from 0 (DMSO) to 5000 ug/ml for 18-19 hours (without an S9 activating fraction) or 5 hours (with S9), and tested for the induction of HPRT mutants by their ability to form colonies in 6-thioguanine (6-TG). Cells were subcultured for 7 days between exposure to the test article and plating in 6-TG to allow for mutation expression. Duplicate cultures were used per concentration, with two trials conducted in the absence of S9 and two trials in its presence. Exposure to the highest concentrations of test article lowered initial survival to 56.3-74.2% of the vehicle-only negative control in the absence of S9 and to 48.2-70.0% in the presence of S9. There was no evidence of a dose-related increase in 6-TG resistance in treated cultures, whereas positive controls were functional. Therefore, the test article was judged nonmutagenic in the

assay. **No adverse effects indicated. Study acceptable** (Vidair 5/12/00).

** 52241-003; 173325; "Mutagenicity Testing of IN A0159-26 in the *Salmonella Typhimurium* Plate Incorporation Assay" (Reynolds, V., E.I. du Pont de Nemours and Co., Inc., Haskell Laboratory for Toxicology and Industrial Medicine, Newark, Del., Project ID No. 250-90, 5/2/90). Test article IN A0159-26 (Haskell No. 18243, > 99% pure) was evaluated for its ability to induce reversion to histidine prototrophy in *Salmonella typhimurium* tester strains TA97, TA98, TA100 and TA1535. Each concentration, from 0 (DMSO) to 5000 ug/plate, was tested in triplicate plates, both in the absence and presence of an activating S9 microsomal fraction. Two independent trials were conducted. Exposure to the test article was for 48 hrs at 37°C. The test article caused slight bacterial toxicity in the absence of S9 (lowering the plating efficiency to about 66% of the negative control), and was nontoxic in the presence of S9. It caused no dose-dependent increase in the revertant frequency. Therefore, it was judged nonmutagenic in the assay. **No adverse effects indicated. Study acceptable** (Vidair 5/15/00).

52241-003; 173326; "Mutagenicity Evaluation of SD 35651 Code-3-11-0-0 Final Report" (Brusick, D., Litton Bionetics, Inc., Kensington, MD, Project No. 2547, 1/16/76). Test article SD 35651 (no lot number or purity provided) was added to cultures of *Salmonella typhimurium* tester strains TA98, TA100, TA1535, TA1537 and TA1538 (all requiring histidine), and to *Saccharomyces cerevisiae* tester strain D_4 (requiring tryptophan), to test for induction of revertants to prototrophy. Four concentrations from 5 to 500 ug/plate were used. A single plate was tested per strain per concentration, in one trial without an S9 activating fraction and in one trial with S9. Vehicle-only negative controls were included, as were positive controls (except for strain D_4 in the presence of S9). Exposure was for 2-3 days at 37°C. No data on cytotoxicity were presented. There was no dose-dependent increase in the number of revertants per plate relative to negative controls, suggesting that the test article is not a mutagen. In contrast, positive controls were functional. **No adverse effects indicated. Study supplemental** (Vidair 5/16/00).

52241-003; 173329; "Mouse Bone Marrow Micronucleus Assay of IN A0159-26" (Reynolds, V., E.I. du Pont de Nemours and Co., Inc., Haskell Laboratory for Toxicology and Industrial Medicine, Newark, Del., Project ID No. 329-90, 8/9/90). At least 5 mice (Crl:CD-(ICR)BR) per sex per dose level were administered test article IN A0159-26 (Haskell No. 18243, > 99% pure) by single-dose oral gavage at 0 (water), 25, 50 and 100 mg/kg. The high dose and negative control animals were sacrificed at 24, 48 and 72 hrs after dosing, while the animals at 25, 50 mg/kg, and positive controls (cyclophosphamide) were sacrificed at 24 hrs post-dosing. Femoral bone marrow was isolated and slides prepared. Samples were stained with acridine orange and examined by fluorescence microscopy. Polychromatic erythrocytes (PCE) and normochromatic erythrocytes (NCE) were counted, and the frequency of micronucleated PCEs determined. High dose animals exhibited lethargy, loss of coordination, gasping, labored respiration, partially closed eyes and face pawing, all within 2 hrs of dosing. Occasional spasms, hunched posture, lacrimation and hair loss followed. Animals dosed at 25 and 50 mg/kg exhibited lethargy, partially closed eyes, labored breathing and hunched posture. There were no consistent dose-related increases in the frequency of micronucleated PCEs in treated animals relative to controls. There were also no significant changes in the PCE/NCE ratio. In contrast, the positive control was functional for PCE micronucleus induction. It was concluded that the test article is inactive in this

assay for chromosome damage. **No adverse effects indicated. Study acceptable** (Vidair 5/22/00).

CHROMOSOME EFFECTS

** 52241-003; 173328; "In Vitro Evaluation of IN A0159-26 for Chromosome Aberrations in Human Lymphocytes" (Stahl, R., E. I. du Pont de Nemours and Co., Inc., Haskell Laboratory for Toxicology and Industrial Medicine, Newark, Del., Project ID No. 258-90, 5/8/90). Human lymphocytes isolated from male and female volunteers were treated with test article IN A0159-26 (Haskell No. 18243, > 99% pure) at 0 (DMSO) to 5.0 mg/ml for 3 hrs at 37°C, followed by washing and incubation for a further 17 hrs, the final 2-3 hrs in the presence of 0.1-0.2 ug/ml of colcemid to facilitate the accumulation of metaphase cells. Fifty metaphases per culture were scored for chromosome and chromatid aberrations, with two cultures per condition (one male and one female). Two trials were performed in the presence of an activating S9 microsomal fraction and two trials in its absence. The test article caused no cell cycle delays as demonstrated by a labeling experiment with 5-bromodeoxyuridine, that distinguished cycles of chromosome replication in individual cells. This finding was supported by measurements of mitotic indices, which were unaffected by the test article. The test article did not cause any dose-dependent increases in chromosome or chromatid aberrations, measured as either aberrations per cell or % of cells with aberrations. Therefore, the test article was judged nonclastogenic. **No adverse effects indicated. Study acceptable** (Vidair 5/19/00).

DNA DAMAGE

** 52241-003; 173327; "Assessment of IN A0159-26 in the *In Vitro* Unscheduled DNA Synthesis Assay in Primary Rat Hepatocytes" (Bentley, K., E.I. du Pont de Nemours and Co., Inc., Haskell Laboratory for Toxicology and Industrial Medicine, Newark, Del., Project ID No. 230-90, 5/14/90). Cultures of primary rat hepatocytes were exposed to test article IN A0159-26 (Haskell No. 18243, > 99% pure) at 0 (DMSO) to 5000 ug/ml in the presence of 5 uCi/ml ^{3}H-thymidine for 18 hrs at 37°C. Duplicate cultures were used per concentration. Following autoradiography, 25 cells per culture were scored for nuclear and cytoplasmic grains, and the net nuclear grains (NNG) calculated. Two independent trials were performed. The test article did not increase the mean NNG/cell. In contrast, the 2-acetylaminofluorene positive controls were functional. Therefore, the test article was judged inactive in this assay for DNA damage and repair. **No adverse effects indicated. Study acceptable** (Vidair 5/16/00).

NEUROTOXICITY

52241-004; 173330; "Acute Neurotoxicity Study of DPX-A0159-31 Administered Orally Via Gavage to Crl: CD BR VAF/Plus Rats" (Foss, J., Argus Research Laboratories, Inc., Horsham, PA, Project ID No. 104-014, 2/1/93). Ten Sprague-Dawley rats (Crl:CD BR VAF/Plus) per sex per dose level were administered test article DPX-A0159-31 (Haskell No. 19548, 99.9% pure) by single-dose oral gavage at 0 (water), 30, 100 and 300 mg/kg. The animals were followed over 14 days for signs of systemic toxicity and neurotoxicity, the latter measured in a functional observational battery (FOB) of tests and

tests of motor activity at 2 hrs, 1, 7 and 14 days post-dosing. There were two female deaths on the day of dosing (day 1, necropsy revealed mottled light to dark red lungs). Mean bodyweights and terminal brain weights of all animals were unaffected by test article administration. Relative food consumption was lower relative to controls in males at 100 mg/kg (days 1-2, $p \leq 0.05$) and 300 mg/kg (days 1-2 $p \leq 0.01$, days 2-3 $p \leq 0.05$, days 3-4 $p \leq 0.05$), and in all treated females at day 1-2 (30 mg/kg $p \leq 0.05$, 100 mg/kg $p \leq 0.01$, 300 mg/kg $p \leq 0.01$). On the day of dosing, mean body temperatures of treated animals exhibited dose-dependent decreases relative to controls ($p \leq 0.01$), recovering in all cases by the next day. FOB measurements on the day of dosing detected the following significant changes relative to controls ($p \leq 0.05$) in high dose males: fewer rears, lower arousal, and increased salivation. Increased fecal boluses were observed in this group on the day after dosing ($p \leq 0.05$), clearing by the next day. FOB parameters in females were more affected. On the day of dosing, females at 100 and 300 mg/kg displayed the following significant changes ($p \leq 0.05$ or $p \leq 0.01$) relative to controls: abnormal home cage behavior, spasms or tremors, fewer rears, more urine pools, ataxic gait, increased palpebral closure, increased salivation, reduced reaction to visual stimuli, reduced reaction to tail pinch, reduced visual placing response, and decreased landing foot splay. By the day after dosing, the only abnormalities in high dose females were increased fecal boluses ($p \leq 0.01$) and increased urine pools ($p \leq 0.01$). By day 8, only increased urine pools ($p \leq 0.05$) were observed in high dose females, clearing by day 15. Treated males had dose-dependent reductions in motor activity relative to controls on the day of dosing only ($p \leq 0.01$). Again, females were more affected, exhibiting dose-dependent reductions in motor activity on the day of dosing ($p \leq 0.01$), the two highest treatment levels showing reductions on day 2 ($p \leq 0.05$), and only the high dose group exhibiting a reduction on day 8 ($p \leq 0.05$), clearing by day 15. Gross necropsy on day 15 was normal, as was neurohistology (high dose animals and controls were examined). **No adverse effects indicated. NOEL (M/F) < 30 mg/kg** (based on lower body temperature and reduced motor activity in both sexes, as well as reduced food consumption in females, all dosed at 30 mg/kg). **Study acceptable** (Vidair 5/17/00).